Remarks and Arguments

Claim 1 was objected to for lacking the article "a" before the word "method" in the claim. Claim 1 has therefore been amended to add "a" at the beginning of the claim, thereby obviating this basis for objection. Reconsideration is respectfully requested.

Claims 13, 20 and 24-26 were rejected under 35 U.S.C. §112, second paragraph, as indefinite. Amendments have been made to these claims to address the specific concerns that the examiner had with each of them, respectively. In light of these amendments, reconsideration of Claims 13, 20 and 24-26 under this ground for rejection is respectfully requested.

Claims 1-20, 25-27 and 29-34 were rejected under 35 U.S.C. §102(e) as being anticipated by U.S. Patent No. 6,436,635 ("Fu"). In making this rejection, the examiner has stated that Fu discloses all of the steps of the rejected claims. However, a close reading of this reference reveals that it differs from the present invention in some very significant ways.

Fu discloses various methods for the detecting and sequencing of double-stranded nucleic acid sequences. Included is the hybridizing of the nucleic acids to an array of probes that each comprise a single-stranded portion, and optional double-stranded portion and a variable sequence within the single-stranded portion. Mass spectroscopy is then used to determine the molecular weights of the hybridized fragments. However, while Fu provides for mass spectroscopy of hybridized oligonucleotide probes and, at times, mentions the use of photocleavage sites, it in no way suggests the use of covalent bonds for immobilization of the probes which are cleavable using photocleavage.

In contrast, the present invention provides an analysis method that uses a chip with spatially separate locations that contain a photocleavable oligonucleotide probe covalently bound to the chip surface for each target sequence to be investigated. The covalent bonding gives the advantages of ease of sample handling and array

production, and the ability to use stringent washing. Meanwhile, the use of a photocleavage site makes the sample much more amenable to analysis using mass spectrometry.

Although Fu mentions the use of a covalent bond and, in other sections of the patent, mentions the use of photocleavable bonds, nowhere is there any suggestion of using the two together. Indeed, they appear to be presented as alternatives. For example, in column 17, lines 21-22, Fu states that "[n]ucleic acid probes may be attached to the solid support by covalent binding, ..." Later in the same paragraph, and alternative is provided, Fu stating that [n]ucleic acids may be attached to the solid support by a photocleavable bond, an electrostatic bond, a disulfide bond, a peptide bond, a diester bond or a combination of these sorts of bonds (column 17, lines 30-33). There is no suggestion that the probe could be both covalently bonded and photocleavable. Example 5, entitled "Attachment of Nucleic Acids Probes to Solid Supports" provides the Fu example of "[c]ovalent attachment of oligonucleotide to derivatized chips..." (column 28, lines 25-26). However, in this example, a subsequent cleavage reaction was not a photocleavage reaction (column 28, lines 53-64).

Claim 1 of the present invention recites a method for the analysis of a sample of genetic material that includes "using a chip with spatially separated locations containing a photocleavable oligonucleotide probe for each target sequence to be investigated, *the probes covalently bound to the chip*" (emphasis added). Nowhere in Fu is there any suggestion of having a probe bound to a chip with a covalent bond and also having the probe photocleavable from the chip. As noted above, this arrangement of the present invention gives it certain significant advantages over the prior art methods. Claims 2-20, 25-27 and 29-34 each depend ultimately from Claim 1, and each is therefore equally unsuggested by the cited prior art. Reconsideration of Claim 1-20, 25-27 and 29-34 under this ground for rejection is respectfully requested.

Claims 21-24 were rejected under 35 U.S.C. §103(a) as being obvious over Fu in view of U.S. Patent No. 6,355,431 ("Chee"). The examiner has cited the Fu reference

for the same reasons as discussed above, but states that Fu does not teach "endonucleolytic cleavage using double strand-specific nuclease RNAseH when there is perfect base pairing, leading to the detection of mismatch and the oligonucleotide probe contains at least one ribonucleotide." The examiner therefore cites Chee, stating that Chee discloses a method having these features, and states that it would have been obvious to combine Fu and Chee. However, without commenting extensively on the content of the Chee reference, it is noted that there is nothing in the combination of Fu and Chee that is any more suggestive of Claim 1, as discussed above, than Fu taken alone. Since each of Claims 21-24 depends ultimately from Claim 1, each of these claims inherits all the limitations of that base claim, including the use of a probe that is covalently bonded to a chip in a photocleavable manner. As such, reconsideration of Claims 21-24 under this ground for rejection is respectfully requested.

Claim 28 was rejected under 35 U.S.C. §103(a) as being obvious over Fu in view of U.S. Patent No. 6,307,039 ("Southern"). The examiner has cited the Fu reference for the same reasons as discussed above in conjunction with Claim 1. However, it was determined that Fu "does not teach the method, wherein the photocleavage site consists of an 0-nitrobenzyl residue." Southern was therefore cited in combination with Fu as showing such a photocleavage site. However, the use by Southern of a particular photocleavable material does not make the combination of Fu and Southern any more suggestive of the invention of Claim 1 than the Fu reference taken alone. Since Claim 28 depends from Claim 1 it inherits all the limitations of that base claim, and is unsuggested by the cited prior art combination for the reasons provided above. Reconsideration of Claim 28 under this ground for rejection is respectfully requested.

In light of the foregoing amendments and remarks, it is respectfully requested that all the claims be allowed such that the application may be passed to issue. If it is believed that a telephone conference will help expedite prosecution of the application, the examiner is invited to call the undersigned. The Commissioner is hereby authorized

to charge any additional fees due for the filing of this paper to applicants' attorneys' Deposit Account No. 02-3038.

Respectfully submitted

Philip L. Conrad Date: April 9, 2003

Philip L. Conrad, Esq. Reg. No. 34,567
KUDIRKA & JOBSE, LLP
Customer Number 021127
Tel: (617) 367-4600 Fax: (617) 367-4656

Version Marked to Show Changes

1. (*Amended*) [Method] A method for the analysis of a sample of genetic material for detailed sequence information contained in a large set of distinct sequences of the sample (the "target sequences"),
comprising the following steps:
(1) producing an amount of nucleic acid templates containing the target sequences by multiplexed amplification of the sample of genetic material,
(2) using a chip with spatially separated locations containing a photocleavable oligonucleotide probe each for each target sequence to be investigated, the probes covalently bound to the chip surface,
(3) modifying, in a single reaction vessel and by using the templates produced in step (1), all oligonucleotide probes on the chip synchronously in a template-dependent manner so that the information under investigation is transferred from the target sequences of the templates to the probes,
(4) cleaving and mass spectrometrically measuring the spatially separated probes, and
(5) extracting the detailed sequence information from the mass measurements of the probes.

13. (*Amended*) The method according to claim 12, wherein insertion and deletion mutations are analyzed [in particular] by the additional template specificity of the reporter oligonucleotides.

20. (*Amended*) The method according to claim 16, wherein single strand mismatches of hybridizations between probes and target sequences [can be identified] are identifiable by template-dependent nuclease digests of the photocleavable probes.

24. (*Amended*) The method according to claim 21, wherein the ribonucleotides of the photocleavable probes [can only be] are template-dependently digested

when there is perfect base pairing, leading to detection of the mismatch in the photocleavable probes.

25. (*Amended*) The method according to claim 9, wherein the hybridization of the target sequences to the photocleavable oligonucleotide probes and their template-dependent modification [can be] are performed cyclicly a number of times.

26. (*Amended*) The method according to claim 25, wherein the enzymes utilized are heat stable and the reaction mixture [can be] is repeatedly warmed directly on the chip.